FDA and the New Paradigm for Tissue Regulation Conference

February 1, 2005

Dallas, Texas

Donor Eligibility Requirements

Ruth Solomon, M.D.

Acting Director

Division of Human Tissues

Office of Cellular, Tissue, Gene Therapies

Center for Biologics Evaluation and Research

Food and Drug Administration

301-827-5363 solomonr@cber.fda.gov

Eligibility Determination for Donors of Human Cells, Tissues and Cellular and Tissue-Based Products

Final Rule

Subpart C of 21 CFR part 1271

Final Rule, cont.

- **Published in Federal Register (69 FR 29786) on May 25, 2004**
- **Effective May 25, 2005, concurrent with effective date of GTP Final Rule**
- **Applies to HCT/Ps procured <u>on or after</u> the effective date**

Suitability Determination for Donors of Human Cellular and Tissue-Based Products Proposed Rule

- **Published September 30, 1999**
- **Comment period closed on Dec. 29, 1999**
- **Reopened on April 18, 2000 for 90 days**
- **> 500 comments—those pertaining to registration or GTP rules are addressed there**

Major Changes from Proposed to Final Rule

- **New Terminology and Definitions**
  - **"Human cellular or tissue-based products" to *"human cells, tissues, and cellular and tissue-based products"***
  - **Donor "suitability" to donor "*eligibility*"**
  - **Changes in definition of "relevant communicable disease agent or disease"**
  - **"Directed donor" to "*directed reproductive donor*"**
  - **Deleted "xenotransplantation" and "close contact" (defined in guidance)**

Changes, cont.

- **New section 1271.47 on procedures for determining donor eligibility**
- **Donor retesting 6 months after donation only applies to anonymous semen donors (not for directed semen donors)**
- **Do not have to test a repeat semen donor at each donation, as long as you do not release the donation unless the donor has been retested at least 6 months post-donation**

Changes, cont.

- **Physical separation between HCT/Ps from ineligible and eligible donors is no longer required; can use other system**
- **Physician no longer has to consent to use of an HCT/P from an ineligible donor**
- **Screening all donors for Treponema pallidum (in addition to testing)**
- **Screening some donors for HTLV-I and II (in addition to testing)**

Changes, cont.

- **Screen all donors for communicable disease risks associated with xenotransplantation (more in guidance)**
- **CMV not considered a “relevant communicable disease agent”, but must test for CMV and have an SOP that describes use of HCT/Ps from a CMV-positive donor**

Changes, cont.

- **If the donor is one month of age or less, you must test a specimen from the birth mother**
- **Timing of specimen collection—7 days before or after recovery; for peripheral blood hematopoietic progenitor/stem cells, 30 days before recovery**
- **Use of a laboratory that has met requirements equivalent to CLIA ’88, as determined by CMS**

Donor Eligibility--General

- **Requirements for determining donor eligibility for all HCT/P donors (with some exceptions) by screening and testing**
- **Part of CGTP requirements**
- **An HCT/P must not be administered until the donor has been determined to be eligible (with some exceptions)**

Donor Eligibility (DE) Determination

- **A donor is eligible if:**
  - **free from risk factors for and clinical evidence of relevant communicable disease agents and diseases,**
  - **free from communicable disease risks associated with xenotransplantation, and**
  - **tests negative or nonreactive for relevant communicable disease agents**

DE Determination, cont.

- **A responsible person must determine and document the eligibility of a donor**

- ***Responsible person*** **means a person who is authorized to perform designated functions for which he or she is trained and qualified**

Relevant communicable disease agent or disease (RCDAD)(1)

- **For all HCT/Ps**
  - **HIV, types 1 and 2**
  - **HBV**
  - **HCV**
  - **Human TSE, including CJD**
  - **Treponema pallidum (agent of syphilis)**
- **For viable, leukocyte-rich HCT/Ps**
  - **HTLV, types I and II**
- **For reproductive HCT/Ps**
  - **Chlamydia trachomatis**
  - **Neisseria gonorrhea**

RCDAD (2)

Another disease/agent that meets these criteria (taken together):

- **There may be a risk of transmission by an HCT/P to recipient or those who come into contact with HCT/P, because**

  (A) the disease agent or disease is potentially transmissible by HCT/P, and

RCDAD (2), cont.

(B) Either of the following applies:

- **Disease agent has sufficient incidence and/or prevalence to affect the potential donor population, or**
- **Disease agent has been released accidentally or intentionally in a manner that could place potential donors at risk of infection**

RCDAD (2), cont.

- **Disease could be fatal, life-threatening, result in permanent impairment or damage, or necessitate medical or surgical intervention to preclude permanent impairment or damage**
- **For which appropriate screening measures have been developed or an appropriate screening test for donor specimens is FDA-licensed, cleared, or approved**

Records that accompany an HCT/P after the DE determination is completed

- **Distinct identification code on container**
- **Statement that donor is eligible (or ineligible)**
- **<u>Summary of records</u>**
  - **Statement that testing done in CLIA-certified (or CMS equivalent) laboratory**
  - **Listing and interpretation of all communicable disease results**
  - **Name and address of establishment that made the DE determination**

Record Retention

- **Name and address of testing laboratory**
- **Results and interpretations of tests**
- **Results and interpretation of screening**
- **DE determination and who made it**
- **Records must be accurate, indelible, legible**
- **Available during FDA inspection**
- **Retain for at least ten years after administration of HCT/P**

Requirements before DE determination is completed

- **Keep HCT/P in quarantine**
- ***Quarantine* means the storage or identification of an HCT/P, to prevent improper release, in a physically separate area clearly identified for such use, or through use of other procedures, such as automated designation**
- **Identify the HCT/P as quarantined pending completion of DE determination**

Requirements before DE is completed, cont.

- **Ship HCT/P in quarantine**
  - **Identify donor by distinct identification code**
  - **State that DE determination is not completed**
  - **State that HCT/P must not be used, except if documented urgent medical need**
  - ***Urgent medical need*** **means that no comparable HCT/P is available and the recipient is likely to suffer death or serious morbidity without the HCT/P**

Use in Urgent Medical Need

- **Information to accompany HCT/P**
  - **Results of any completed screening/testing**
  - **List of screening/testing not completed**
- **Label: "Not evaluated for infectious substances" and "Warning: Advise patient of communicable disease risks"**
- **Document that you notified physician that screening and testing were not completed**
- **Complete DE determination and inform physician of results**

HCT/Ps from ineligible donors

- **Store in a physically separate area identified for such use or follow other procedures adequate to prevent improper release, such as automated designation, until destruction or other disposition---**
- **Limited uses of HCT/Ps from ineligible donors are not prohibited:**
  - **Allogeneic use in a first-degree or second-degree blood relative**
  - **Reproductive cells or tissue from a directed reproductive donor**
  - **Documented urgent medical need**

Ineligible donors, cont.

- **Label: Biohazard legend and “Warning: Advise patient of communicable disease risks” and “Warning: Reactive test results for (name of disease agent or disease)” --if applicable**
- **Document that you notified physician of results**

Non-clinical use

Label: Biohazard legend and “For nonclinical Use Only”

Donor Screening

- **Review the relevant medical records for**
  - **Risk factors for, and clinical evidence of RCDAD**
  - **Communicable disease risks associated with xenotransplantation**
- **Abbreviated procedure for repeat donor**
  - **Determine and document any changes since the previous donation that would make the donor ineligible**
  - **Do a complete donor screening at least every 6 months**

Relevant Medical Records

- **Current donor medical history interview**
- ***Donor medical history interview*** **means a documented dialogue about the donor's medical history and relevant social behavior (activities, behaviors and descriptions considered to increase the risk of RCDAD), with the donor if living and able to participate, or if not, with an individual(s) able to provide the information sought**

Relevant medical records, cont.

- **Current report of physical assessment of a cadaveric donor or physical examination of a living donor**
- ***Physical assessment of a cadaveric donor*** **means a limited autopsy or recent antemortem or postmortem physical examination to assess for signs of RCDAD and for signs suggestive of a risk factor for a RCDAD**

Relevant medical records, cont.

- **And if available, the following:**
  - **Laboratory test results (other than for RCDAD)**
  - **Medical records**
  - **Coroner and autopsy reports**
  - **Records or other information received from any source pertaining to risk factors for RCDAD (e.g., social behavior, clinical signs and symptoms, treatments related to medical conditions suggestive of risks for RCDAD)**

Donor Testing

- **To adequately and appropriately reduce the risk of transmission of RCDAD, you must test a donor specimen for evidence of infection due to communicable disease agents**
- **For a donor 1 month of age or younger, test a specimen from the birth mother**
- **Timing of specimen collection—7 days before or after recovery; for donors of peripheral blood hematopoietic stem cells, 30 days before recovery**

Donor Testing, cont.

- **Use appropriate FDA-licensed, approved or cleared donor screening tests, in accordance with the manufacturer's instructions**
  - **To test for Chlamydia trachomatis and Neisseria gonorrhea, use a diagnostic test labeled for detection of those organisms in an asymptomatic, low-prevalence population**
- **Use a test specifically labeled for cadaveric specimens when applicable and when available**
- **www.fda.gov/cber/tissue/prod.htm**

Donor Testing, cont.

- **Use a laboratory that is certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments (CLIA-certified) or one that has met equivalent requirements as determined by Center for Medicare and Medicaid Services (CMS)**

Donor Testing, cont.

- **<u>For all HCT/P donors</u>**
  - **HIV, types 1 and 2**
  - **HBV**
  - **HCV**
  - **Treponema pallidum (agent of syphilis)**
- **<u>For viable, leukocyte-rich HCT/P donors</u>**
  - **HTLV, types I and II**
  - **CMV—if reactive, the donor is not automatically ineligible; establish and maintain a standard operating procedure governing the release of an HCT/P from a donor whose specimen tests reactive for CMV**

Donor Testing, cont.

- **<u>For reproductive HCT/Ps</u>**
  - **Chlamydia trachomatis**
  - **Neisseria gonorrhea**

  Retesting anonymous semen donors:
  - **At least 6 months after the date of donation of semen, collect a new specimen from the donor and test it**
  - **Semen remains in quarantine until repeat test is negative or non-reactive**

Donor Testing, cont.

- **Donor is ineligible if:**

- **Donor screening test is reactive**
  - **except if a non-Treponemal screening test is reactive and a specific Treponemal confirmatory test is negative, or**
- **Plasma dilution sufficient to affect test results is suspected**
  - **Unless a pre-transfusion/infusion specimen tests negative, or**
  - **An appropriate algorithm is used to show that plasma dilution sufficient to affect test results has not occurred**

Suspicion of Plasma Dilution

- **Donor is over 12 years of age**
  - **Blood loss is known or suspected**
  - **>2000mL of blood or colloids in 48 hr, or**
  - **>2000mL of crystalloids in 1 hr.**

- **Donor is 12 years of age or younger**
  - **Blood loss may or may not have occurred**
  - **Any amount of blood or colloids in 48 hr, or**
  - **Any amount of crystalloids in 1 hr**

Exceptions to Requirement for DE Determination

- **DE determination is not required for**
  - **Autologous use**
  - **Reproductive HCT/Ps donated by a sexually intimate partner of recipient**
  - **Cryopreserved reproductive HCT/Ps, originally exempt at time of donation, that are subsequently intended for directed donation, provided that additional donations are unavailable and the donors are now screened and tested**

Exceptions, cont.

- **Required labeling**
  - **“For autologous use only” if appropriate**
  - **“Not evaluated for infectious substances” and “Warning: Advise patient of communicable disease risks” (for autologous use, this last statement can be omitted)**
  - **Biohazard legend and “Warning: Advise patient of communicable disease risks” if any screening performed indicates risk factors for or clinical evidence of RCDAD, and if test is reactive, also include “Warning: Reactive test results for (name of RCDAD)”**